on the reactivity of the patient sample with [different] the Ro/SSA peptides.

Remarks

Withdrawal of many of the previous rejections under 35 U.S.C. §112 is greatly appreciated.

Objections to Title and Specification

The title and the references to trademarks have been amended as requested by the Examiner.

Claims 4 and 5 have also been cancelled.

Rejections under 35 U.S.C. §112

The specification has been objected to and claims 1-3 and 10-16 rejected under 35 U.S.C. §112. This rejection is respectfully traversed.

The discussion on page 4 of the office action is confusing. It is well established that antibodies bind to epitopes which are formed by five to eight amino acids; see, for example, "Molecular Biology of the Gene" Watson, et al., 4th edition, page 836 (Benjamin/Cummings Publishing Co. 1987), a copy of which is enclosed.

The Examiner's attention is also drawn to page 32 of "General Immunology" by Herman N. Eisen (Lippincott, 1990), a copy of which is enclosed. The discussion at column 1 supports applicants' position that the peptides are representative of those linear segments of the intact protein (i.e., the continuous

epitopes) which are bound by antibody, and that the method used to identify the claimed peptides "cannot be expected to succeed when an epitope is discontinuous". Accordingly, the peptides that are claimed must include linear or continuous epitopes bound by antibody which would be independent of the length of the peptide.

The comment that a peptide of lesser or greater length than an octapeptide would not share sequence with the octapeptide does not make sense: if one took a peptide of XXXXXXXX and removed one or two amino acids from the end, the peptide should still have the sequence of XXXXXX. Similarly, if one added amino acids to the octapeptide to make a peptide of 40 amino acids, the peptide would still include the sequence XXXXXXXX and would therefore still bind the antibody. Since the only epitopes claimed are those that are linear or continuous, adding amino acids to the end(s) of the octapeptide should not alter binding. There is no support for the *allegation* that additions of amino acids to the peptide would prevent binding under all conditions - applicants have indeed provided evidence that additions to the peptides, as well as minor deletions or substitutions - do not.

Once applicants have rebutted the argument that the claims are non-enabling with data, the Examiner must provide evidence; not maintain mere allegations to the contrary. No evidence to support the Examiner's position has been provided.

See the Proposed Utility Examination Guidelines, page 5, for example.

With respect to binding, it is again respectfully brought to the Examiner's attention that **all of the claimed peptides were identified by binding with autoantibodies to Ro/SSA from patients with autoimmune diseases.** Accordingly, applicants have shown that all of the claimed peptides are useful to identify patients with autoantibodies to Ro/SSA.

Moreover, as previously explained and demonstrated, the presence of autoantibodies to Ro/SSA is diagnostic for autoimmune disease. **Any antibodies to Ro/SSA is abnormal and associated with disease.** Therefore, all of the claimed peptides are useful in predicting whether or not a patient has an autoimmune disease. **The greater the levels of antibody to Ro/SSA, the worse the prognosis of the disease.** The Examiner's attention is directed to the papers cited at pages 2 and 3 of the application, copies of which were submitted with the Information Disclosure Statement, showing that there is a correlation in severity of disease with the antibody titer. See, for example, Harley, J.B., A.L. Sestak, L. Willis, S.M. Fu, J. Hanson, M. Reichlin "Model for Disease Heterogeneity in Systemic Lupus Erythematosus. Relationships between histocompatibility antigens, autoantigens, and lymphopenia on renal disease" (1989) Arthritis Rhuematism 39, 826-836. However, to facilitate prosecution, claim 16 has been

amended to define the process as referring to the claimed peptides as Ro/SSA peptides.

With respect to the issue of the breadth of autoimmune disorders, the Examiner's position is well taken and claim 12 has been amended to define the patients as those having autoantibodies to Ro/SSA.

Rejections under 35 U.S.C. §103

Claims 1-3 and 10-16 were rejected under 35 U.S.C. §103 as obvious over Deutscher, et al., Proc. Natl. Acad. Sci. USA 85, 9479-9483 (1988) in view of U.S. Patent No. 5,312,752 to Wotiz, et al., Voller, et al., Manual of Clin. Lab. Immunol. Chap. 17 (1986) and Geysen, et al. J. Immunol. Methods. 102, 259-271 (1987). These rejections are respectfully traversed.

It should be noted that this rejection was raised in the Office Action mailed October 19, 1993, and withdrawn in the Office Action mailed June 27, 1994.

Wotiz, et al.

Wotiz, et al., discloses antibodies immunoreactive with the DNA-binding domain of the estrogen receptor protein. The disclosure is specific to estrogen receptor proteins. The zinc finger referred to by the Examiner consists of a region of at least 40 amino acids. **Only a few amino acids are conserved in any claimed peptide.** Please note the use by Wotiz, et al., of the language at col. 16, lines 61-64, "furthermore, this region

is ***thought*** *to have the conserved cysteine and histidine residues* which may be involved in the formation of the zinc-fing-like structures of the proteins". (emphasis added) Based on the Examiner's comments regarding the uniqueness of this region to the human estrogen receptor, and the **lack of crossreactivity of polyclonal antibodies to other proteins**, it would appear that this region is inherently different from and could not make obvious the claimed peptides with are **immunoreactive with Ro/SSA, not the estrogen receptor**.

Deutscher, et al.

Deutscher, et al., describes the nucleic acid and amino acid sequences of Ro/SSA. There is no disclosure regarding the antigenicity of any portion of the protein, nor does Deutscher, et al., suggest determining if any one or more particular peptide fragments of the protein are immunoreactive with autoantibody.

It is well established that it is the secondary and tertiary structures of proteins which form the eptiopes that are specifically reactive with antibodies. Accordingly, one would not be motivated from this publication to look for peptides which are specifically reactive.

Voller, et al.

Voller, et al., describes enzyme-linked immunsorbent assays using antigen and enzyme labelled antibody. There is no

disclosure that one should use octapeptides from a large autoantigen to make a diagnostic assay.

Geyson, et al.

Geyson, et al., discloses a method by applicants to identify the claimed peptides, but which has not been successfully used by others due to technical difficulties and lack of reproducibility. See, for example, Miller, F.W., K.A. Waite, T. Biswas, P.H. Plotz, "Role of an Autoantigen, Histidyl-tRNA Synthase, in the Induction and Maintenance of Autoimmunity" (1990) Proc. Natl. Acad. Sci. USA 87, 9033-9037. Miller, et al., made hexapeptides of another autoantigen, histidyl tRNA synthase, which is present in approximately 30% of patients with polymyositis. They were unable to obtain any peptides bound by the naturally occurring autoantibodies.

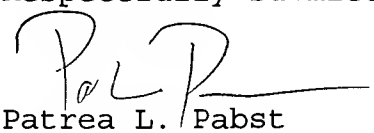
It is not obvious that one would be able to use the method of Geyson, et al., with any degree of predictability with any large protein, especially a large autoantigen such as Ro/SSA. It may be that tertiary structure is the controlling factor in determining the specificity of the naturally occurring autoantibodies, rather than secondary and tertiary structure. Applicants did determined that certain peptides derived from Ro/SSA are reactive with naturally occurring autoantibodies and are therefore useful in diagnosis of patients. This could not have been obvious to one of ordinary skill in the art, from the

cited publications, as of the time this application was filed. Only by actually synthesizing and testing each peptide can one determine which, if any, peptides derived from the full length protein, will be reactive.

In summary, none of the art suggests that the large autoantigen, Ro/SSA, could be partioned into overlapping octapeptides that would be reactive with naturally occurring autoantibodies, nor that the binding would be sufficiently strong and specific to be useful in a diagnostic assay. It is not enough under §103 to use hindsight after applicant has disclosed his invention to piecemeal together the prior art to yield the claimed invention: it must be obvious from the combination of the prior art, as a whole, that one of ordinary skill in the art **should** combine the cited art and would have a **reasonable expectation of success in obtaining the claimed invention**. The art does not do this.

Allowance of all claims 1-3 and 10-16, as amended, is earnestly solicited.

Respectfully submitted,



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AMENDMENT

CERTIFICATE OF MAILING UNDER 37 CFR §1.8a

I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Date: June 28, 1995

Patrea Pabst